

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A2	(11) International Publication Number: WO 99/55672 (43) International Publication Date: 4 November 1999 (04.11.99)
C07D 209/08, 209/34, 403/12, A61K 31/40		
(21) International Application Number: PCT/US99/09132		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 28 April 1999 (28.04.99)		
(30) Priority Data: 09/069,129 29 April 1998 (29.04.98) US		
(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).		
(72) Inventors: KELLY, Michael, Gerard; 19 Clinton Court, Plainsboro, NJ 08536 (US). KANG, Young, Hee; 324 Andover Place, Robbinsville, NJ 08691 (US).		
(74) Agents: ECK, Steven, R.; American Home Products Corporation, Patent Law Dept. – 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.		
		Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: ANTIPSYCHOTIC INDOLYL DERIVATIVES		
		<p style="text-align: right;">(1)</p>
(57) Abstract		
		<p>The present invention provides novel compounds of general formula (1), wherein R₁ and R₂ are H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, OR₅, nitro, amino, CF₃ or R₁ and R₂ are taken together to form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group; R₃ represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen; R₄ represents a group selected from hydrogen, 1 to 6 carbon alkyl or R₅; R₅ is CH₂Ph in which the phenyl ring can be optionally substituted by a group selected from OMe, halogen, CF₃; X is selected from a group represented by N, CR₄, CHR₄ and CHCH; A is selected from a group represented by N, NH, CH and CH₂; B is selected from a group represented by =O, =S, H and H₂; or A and B may be concatenated together to form indole, benzimidazole, indolone or indoline moieties; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions and methods of treating central nervous system disorders utilizing these compounds.</p>

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

ANTIPSYCHOTIC INDOLYL DERIVATIVES

This application claims the benefit of U.S. Provisional Application No. 60/104,596, which was converted from U.S. Patent Application No. 09/069,129, filed 5 April 29, 1998, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

This invention concerns a series of novel β -hydroxy aryloxypropylamines which are effective pharmaceuticals for the treatment of conditions related to or affected by the dopamine D₂ receptor and also by the serotonin 1A receptor subtype. The 10 compounds are particularly useful for the treatment of schizophrenia and related psychotic disorders and other conditions such as Parkinson's disease and Alzheimer's disease.

Background to the Invention

15

In their letter to the editor, TINS, Vol. 17, No. 4, 1994, Bowen et al. note that the cognitive impairment characteristics of Alzheimer's disease may be ameliorated by antagonists at the inhibitory 5-HT_{1A} receptor, or by activation of the phospholipase-C-linked cholinergic M₁ receptor.

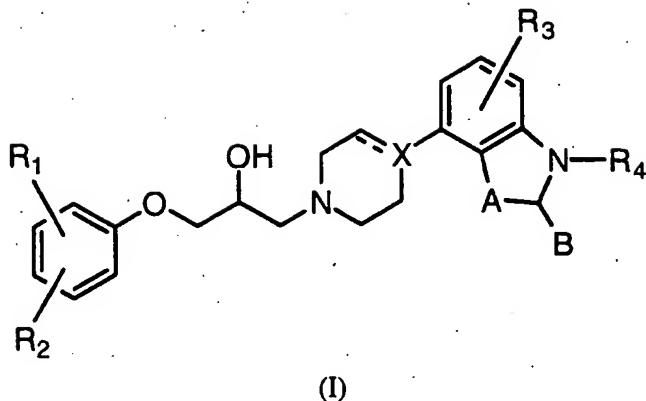
20

Summary of the Present Invention

This invention relates to novel indolyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy. The compounds are useful for the treatment of psychotic disorders, particularly schizophrenia, by virtue of their ability to antagonize the dopamine D₂ receptor. Furthermore, the present invention also provides compounds that are antagonists and agonists at the 5-HT_{1A} receptor subtype and thus compounds of this invention may be used to treat Alzheimer's Disease, Parkinson's Disease, depression and anxiety.

30
Compounds of the present invention are represented by the general formula (I),

- 2 -



wherein

R₁ and R₂ are each independently selected from H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, arylalkyl, aralkyloxy, OR₅, nitro, amino, CF₃ and when R₁ and R₂ are taken together, form a fused ring at the 1,2- or 5
5 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-
2,3-substituted indole group, or a 4- or 5- or 8-substituted quinoline group, the substituents
2,3 on the indole or quinoline groups being selected from halogen, C₁-C₆ alkyl, C₁-C₆
10 alkoxy, -S-C₁-C₆ alkyl, -CN, -OH, -NO₂ or -CF₃;

R₃ represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen;

R₄ represents a group selected from hydrogen, 1 to 6 carbon alkyl or R₅;

R₅ is CH₂Ph in which the phenyl ring can be optionally substituted by a group
15 selected from OMe, halogen, CF₃;

X is selected from a group represented by N, CR₄, CR₄ and CHCH;

A is selected from a group represented by N, NH, CH and CH₂;

B is selected from a group represented by =O, =S, H and H₂;

or A and B may be concatenated together to form indole, benzimidazole, indolone or
20 indoline moieties;

or a pharmaceutically acceptable salt thereof.

It will be understood that the type of substitution indicated by B in the generic groups herein will be controlled by whether A is N, NH, CH or CH₂.

25

The term "aryl" as used in the definitions of R₁ and R₂ indicates phenyl, or pyridine groups, optionally substituted by from 1 to 3 substituents selected from

- 3 -

halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -S-C₁-C₆ alkyl, -CN, -OH, -NO₂ or -CF₃. The most preferred aryl group is phenyl, optionally substituted as just described. The most preferred arylalkyl group in the definitions above is benzyl and the preferred aralkyloxy group is benzyloxy.

5

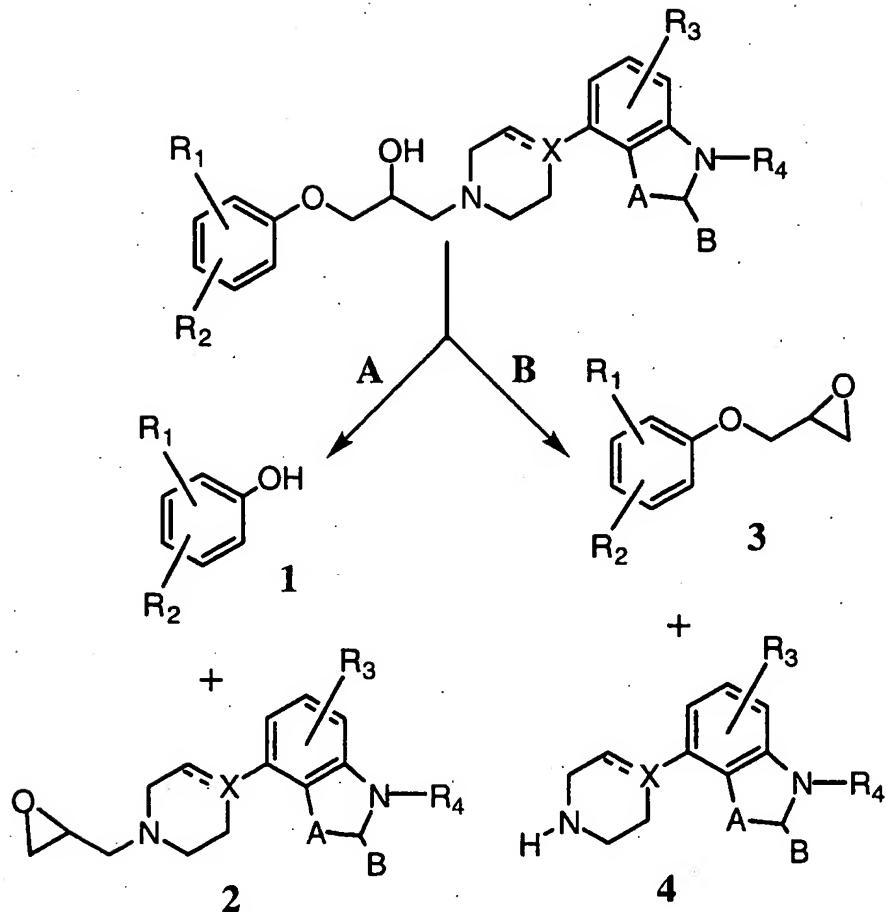
The pharmaceutically acceptable salts are the acid addition salts which can be formed from a compound of the above general formula and a pharmaceutically acceptable inorganic acid such as phosphoric, sulfuric, hydrochloric, hydrobromic citric, maleic, fumaric, acetic, lactic or methanesulfonic acid.

10

Detailed Description of the Invention

Compounds of the present invention may be prepared using conventional methods, utilizing for example the disconnections shown in scheme A and scheme B 15 below.

- 4 -



In scheme A, the phenol 1 is reacted with an epoxide of formula 2 to afford the required product. The starting phenol may be commercially available or can be readily obtained by those practiced in the art of organic synthesis. The epoxide 2 is available for example, from the reaction of an amine of formula 4 with optically active or racemic epichlorohydrin or glycidyl tosylate.

In scheme B, the epoxide 3 can be obtained from the reaction of a phenol of formula 1 with optically active or racemic epichlorohydrin or glycidyl tosylate. Reaction of this compound with an amine of formula 4 affords the required product. The product can then be used to form a pharmaceutically acceptable addition salt.

Compounds of the present invention bind with very high to the 5-HT1A receptor and the dopamine D2 receptor and consequently, they are useful for the

- 5 -

treatment of central nervous system disorders such as schizophrenia, depression, anxiety, including generalized anxiety, sleep disorders, sexual dysfunction, alcohol and cocaine addiction, and related problems in addition to the treatment of Alzheimer's disease, Parkinson's disease, obesity and migraine. The present compounds can also
5 be used in regimens to increase cognition enhancement. This invention includes methods of treating in mammals each of these maladies, as well as a method of increasing cognition enhancement, the methods comprising administering to a mammal in need thereof an effective amount of one or more of the compounds of this invention, or a pharmaceutically acceptable salt thereof.

10

It is understood that the therapeutically effective dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. Variables involved include the specific psychosis or state of anxiety and the size, age and response pattern of the patient. The novel method of the invention for
15 treating conditions related to or are affected by the reuptake of serotonin comprise administering to warm-blooded animals, including humans, an effective amount of at least one compound of this invention or a non-toxic, pharmaceutically acceptable addition salt thereof. The compounds may be administered orally, rectally, parenterally, or topically to the skin and mucosa. The usual daily dose is depending on
20 the specific compound, method of treatment and condition treated. An effective dose of 0.01 - 1000mg/Kg may be used for oral application, preferably 0.5 - 500 mg/Kg, and an effective amount of 0.1 - 100 mg/Kg may be used for parenteral application, preferably 0.5 - 50 mg/Kg.

25

The present invention also includes pharmaceutical compositions containing a compound of this invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

30

Applicable solid carriers or excipients can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintergrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in
35 the shape and size desired. The powders and tablets preferably contain up to 99% of

- 6 -

the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

5

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier 10 can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium 15 carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

20

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

25

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or 30 sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

- 7 -

The affinity of drugs for the dopamine receptor was established by testing the claimed compound's ability to displace [³H]-Spiperone binding in CHO cells stably transfected with the human dopamine D₂ receptor. CHO cells expressing the human dopamine D₂ receptor were cultured in suspension by expansion (every 3 - 4 days) in a serum free media to provide approximately 7.5 x 10⁵ cells/ml. The cells were harvested by centrifugation (900 x g for 10 min.), resuspended in half volume of 1X dulbecco PBS solution at pH 7.4, and after a further recentrifugation, the cell pellet was resuspended in 50 mM Tris.HCl (pH 7.4) containing 1.5 mM CaCl₂, 5.0 mM EDTA, 5.0 mM KCl, 120 mM NaCl, 1.0 mM PMSF and 1.0 mg % leupeptin. The cells were homogenized, centrifuged at 40,000 x g for 30 minutes and resuspended in fresh buffer (10 ml), and the process repeated twice. The final pellet was suspended in a volume of 50.0 mM Tris.HCl sufficient to give a protein concentration of 125.0 µg/ml of membrane suspension. The binding assay is performed in a 96 well microtiter plate. 100 µl of buffer is added to the wells, and those receiving a displacer for nonspecific binding (NSB) assessment or test compounds receive 80 µl of incubation buffer. [³H]-Spiperone (S.A. 89 - 100 Ci/mmole) is used as ligand and 0.5 nM in 20 µl volume is added to all wells, followed by the addition of the displacer D-butaclamol (1µM in 20 µl) for nonspecific binding determination. The reaction is initiated by the addition of 80 µl of the tissue membrane, and after 120 minutes at room temperature the wells are harvested using a Brandell® Harvester onto glass fiber filter presoaked in 0.1% polyethylimine. After washing three times with cold 50 mM Tris.HCl, the filter mat is oven dried and sealed in an envelope with melted multitex for scintillation counting in a Wallac 1205 BetaPlate Counter. The data is analyzed and Ki values are computed for active compounds. Using this assay, the following Ki's were determined for a series of standard D₂ receptor ligands.

	Compound	D ₂ binding Ki (nM)
	Spiperone	0.08
30	Clozapine	28.6
	Haloperidol	0.57
	7-OHDPAT	96
	Sulpiride	49.4

The results for a number of examples of compounds of formula 1 in this standard experimental test procedure were as follows

Compound	D2 binding
5	Ki (nM)
Example 2	33.5
Example 5	31.9
Example 6	10.4

10 High affinity for the serotonin 5-HT_{1A} receptor was established by testing the claimed compound's ability to displace [³H] 8-OH-DPAT binding in CHO cells stably transfected with human 5HT1A receptor. Stably transfected CHO cells are grown in DMEM containing 10% heat inactivated FBS and non-essential amino acids. Cells are scraped off the plate, transferred to centrifuge tubes, and washed twice by
15 centrifugation (2000 rpm for 10 min., 4°C) in buffer (50 mM Tris pH 7.5). The resulting pellets are aliquoted and placed at -80°C. On the day of assay, the cells are thawed on ice and resuspended in buffer. The binding assay is performed in a 96 well microtiter plate in a total volume of 250 µL. Non-specific binding is determined in the presence of 10 mM 5HT, final ligand concentration is 1.5 nM. Following a 30 minute
20 incubation at room temperature, the reaction is terminated by the addition of ice cold buffer and rapid filtration through a GF/B filter presoaked for 30 minutes in 0.5% PEI. Compounds are initially tested in a single point assay to determine percent inhibition at 1, 0.1, and 0.01 mM, and Ki values are determined for the active compounds.

- 9 -

	Compound	5-HT1A binding
		Ki (nM)
	Example 1	6.0
	Example 2	7.6
5	Example 3	1.8
	Example 4	8.8
	Example 5	12.1
	Example 6	10.4
	Example 7	7.2
10	Example 8	4.5

The following non-limiting specific examples are included to illustrate the synthetic procedures used for preparing compounds of the formula 1. In these examples, all chemicals and intermediates are either commercially available or can be prepared by standard procedures found in the literature or are known to those skilled in the art of organic synthesis.

Example 1

1-(1H-Indol-4-yloxy)-3-[4-(1H-indol-4-yl)

piperazin-1-yl]-propan-2-ol

A methanolic solution (20 ml) of 1-(indole-4-oxy)-2,3-epoxypropane (0.38 g, 2.0 mmole) was added dropwise under a nitrogen atmosphere to a stirred solution of 1-(indol-4-yl)-piperazine (0.4 g, 2.0 mmole) in methanol (75 ml). The mixture was heated to reflux for 2 hrs, concentrated in vacuo, and the product purified by column chromatography over silica gel ($\text{CH}_2\text{Cl}_2:\text{MeOH}$ 95:5) to afford an oil (0.7g, 90% yield). Treatment with a 0.25M ethanolic fumaric acid solution gave the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

30 m.p. 147-150°C

Elemental Analysis for: C₂₃H₂₆N₄O₂. 1.0C₄H₄O₄

Calculated: C, 64.02; H, 5.97; N, 11.06

Found: C, 64.59; H, 6.36; N, 11.81

- 10 -

Example 2

1-(4-Chloro-phenoxy)-3-[4-(1H-indol-4-yl)
piperazin-1-yl]-propan-2-ol

5 A methanolic solution (75 ml) of 4-chlorophenyl-2,3-epoxypropyl ether (0.55 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc:Hexane 90:10) to afford a white solid (1.25 g, 100%). Treatment with a 0.25M ethanolic fumaric acid solution gave the
10 required product, which was recrystallized from ethanol to afford the title compound as a white solid.
m.p. 224-225°C
Elemental Analysis for: C₂₁H₂₄ClN₃O₂. 0.5C₄H₄O₄
Calculated: C, 62.23; H, 5.9; N, 9.47
15 Found: C, 61.98; H, 5.79; N, 9.21

Example 3

1-[4-(1H-Indol-4-yl)-piperazin-1-yl]-3-
(4-methoxy-phenoxy)-propan-2-ol

20 A methanolic solution (75 ml) of 4-methoxyphenyl-2,3-epoxypropyl ether (0.54 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH₂Cl₂:MeOH 90:10) to afford a white solid (1.1 g, 96%). Treatment with a 0.25M ethanolic fumaric acid solution gave the
25 required product, which was recrystallized from ethanol to afford the title compound as a white solid.
m.p. 226-227°C
Elemental Analysis for: C₂₂H₂₇N₃O₃. 0.5C₄H₄O₄
30 Calculated: C, 65.59; H, 6.65; N, 9.56
Found: C, 65.36; H, 6.48; N, 9.36

- 11 -

Example 4

1-[4-(1H-Indol-4-yl)-piperazin-1-yl]-3-(4-nitro-phenoxy)-propan-2-ol

5 A methanolic solution (65 ml) of 1,2-epoxy-3-(4-nitrophenoxy)-propane (0.59 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo to afford the product as a yellow solid (1.1 g, 93%). Treatment with a 4M ethereal HCl solution gave the required product, which was recrystallized from ethanol to afford the title compound
10 as a light yellow solid.

m.p. 248°C

Elemental Analysis for: C₂₁H₂₄N₄O₄. 1.0HCl

Calculated: C, 58.26; H, 5.82; N, 12.94

Found: C, 57.92; H, 5.76; N, 12.66

15

Example 5

1-(2-Chloro-phenoxy)-3-[4-(1H-indol-4-yl)piperazin-1-yl]-propan-2-ol

20 A methanolic solution (75 ml) of 1-(2-chlorophenoxy)-2,3-epoxypropane (0.55 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH₂Cl₂:MeOH 90:10) to afford a white solid (1.09 g, 94%). Treatment with a 0.25M ethanolic fumaric acid solution gave the
25 required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 207°C

Elemental Analysis for: C₂₁H₂₄ClN₃O₂. 0.5C₄H₄O₄

Calculated: C, 62.23; H, 5.9; N, 9.47

30 Found: C, 62.13; H, 5.72; N, 9.34

- 12 -

Example 6

1-(4-Fluoro-phenoxy)-3-[4-(1H-indol-4-yl)
piperazin-1-yl]-propan-2-ol

5 A methanolic solution (50 ml) of 1-(4-fluorophenoxy)-2,3-epoxypropane (0.50 g, 3.0 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 1 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc) to afford a white solid (1.1 g, 99%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required salt, 10 which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 234-235°C

Elemental Analysis for: C₂₁H₂₄FN₃O₂. 0.5C₄H₄O₄

Calculated: C, 64.62; H, 6.13; N, 9.83

Found: C, 64.38; H, 6.01; N, 9.67

15

Example 7

4-{2-Hydroxy-3-[4-(1H-indol-4-yl)-piperazin-1-yl]
propoxy}-1H-indole-2-carboxylic acid amide

20 A methanolic solution (50 ml) of 1-(2-carboxamidoindol-4-oxy)-2,3-epoxypropane (0.83 g, 1.5 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 0.5 hr under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (CH₂Cl₂:MeOH 90:10) to afford a white solid (1.24 g, 97%). Treatment with a 1.0M ethereal HCl solution gave 25 the required product, which was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 258-259°C

Elemental Analysis for: C₂₄H₂₇N₅O₃. 1.0HCl

Calculated: C, 60.5; H, 6.08; N, 14.7

30 Found: C, 60.31; H, 5.89; N, 14.6

- 13 -

Example 8

1-(Biphenyl-2-yloxy)-3-[4-(1H-indol-4-yl)
piperazin-1-yl]-propan-2-ol

5 A methanolic solution (50 ml) of 2-biphenylglycidyl ether (0.68 g, 1.5 mmole) and 1-(indol-4-yl)-piperazine (0.6 g, 3.0 mmole) was refluxed for 15 hrs under an atmosphere of nitrogen. The mixture was concentrated in vacuo, and the product purified by silica gel chromatography (EtOAc) to afford a white solid (1.23 g, 96%). Treatment with a 0.25M ethanolic fumaric acid solution gave the required salt, which
10 was recrystallized from ethanol to afford the title compound as a white solid.

m.p. 214-215°C

Elemental Analysis for: C₂₇H₂₉N₃O₂. 1.0C₄H₄O₄

Calculated: C, 68.49; H, 6.12; N, 7.73

Found: C, 68.6; H, 6.12; N, 7.88

15

Example 9

1-(1H-Indol-4-yloxy)-3-[4-(1H-benzimidazole-4-yl)
piperazin-1-yl]-propan-2-ol

20 The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-benzimidazole-4-yl)piperazine (2 mmole) according to the above procedures.

25

Example 10

1-(1H-Indol-4-yloxy)-3-[4-(1H-2,3-dihydroindol-4-yl)
piperazin-1-yl]-propan-2-ol

30 The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-2,3-dihydroindol-4-yl)piperazine (2 mmole) using the procedures outlined in the previous examples.

- 14 -

Example 11

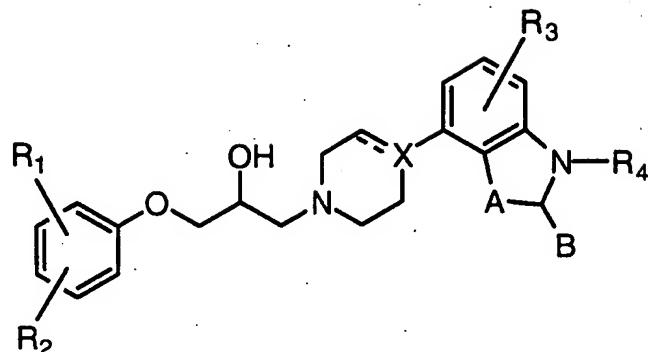
1-(1H-Indol-4-yloxy)-3-[4-(1H-2-oxindol-4-yl)
piperazin-1-yl]-propan-2-ol

5 The title compound is prepared from the reaction of 1-(indole-4-oxy)-2,3-epoxypropane (2.0 mmole) and 1-(1H-2-oxindol-4-yl)piperazine (2 mmole) using the procedures outlined in the previous examples.

- 15 -

We claim:

1. A compound according to the formula;



5 wherein

R_1 and R_2 are each independently selected from H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, arylalkyl, aralkyloxy, OR₅, nitro, amino, CF₃ and when R_1 and R_2 are taken together, form a fused ring at the 1,2- or 10 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7- substituted indole group, or a 4- or 5- or 8-substituted quinoline group, the substituents on the indole or quinoline groups being selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -S-C₁-C₆ alkyl, -CN, -OH, -NO₂ or -CF₃;
15 or R_1 and R_2 are taken together, form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group;

R_3 represents a group selected from hydrogen, a 1 to 6 carbon alkyl, a 1 to 4 carbon alkoxy or a halogen;

R_4 represents a group selected from hydrogen, 1 to 6 carbon alkyl or R_5 ;

R_5 is CH₂Ph in which the phenyl ring can be optionally substituted by a group 20 selected from OMe, halogen, CF₃;

X is selected from a group represented by N, CR₄, CR₄ and CHCH;

A is selected from a group represented by N, NH, CH and CH₂;

B is selected from a group represented by =O, =S, H and H2;

or A and B may be concatenated together to form indole, benzimidazole, indolone or 25 indoline moieties;

or a pharmaceutically acceptable salt thereof.

- 16 -

2. A compound of claim 1 which is 1-(1H-indol-4-yloxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
3. A compound of claim 1 which is 1-(4-chloro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
4. A compound of claim 1 which is 1-[4-(1H-indol-4-yl)-piperazin-1-yl]-3-(4-methoxy-phenoxy)-propan-2-ol
- 10 5. A compound of claim 1 which is 1-[4-(1H-indol-4-yl)-piperazin-1-yl]-3-(4-nitro-phenoxy)-propan-2-ol or a pharmaceutically acceptable salt thereof.
- 15 6. A compound of claim 1 which is 1-(2-chloro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
7. A compound of claim 1 which is 1-(4-fluoro-phenoxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
- 20 8. A compound of claim 1 which is 4-{2-hydroxy-3-[4-(1H-indol-4-yl)-piperazin-1-yl]propoxy}-1H-indole-2-carboxylic acid amide or a pharmaceutically acceptable salt thereof.
9. A compound of claim 1 which is 1-(biphenyl-2-yloxy)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
- 25 10. A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-benzimidazole-4-yl)piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
- 30 11. A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-2,3-dihydroindol-4-yl) piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.
- 35 12. A compound of claim 1 which is 1-(1H-Indol-4-yloxy)-3-[4-(1H-2-oxindol-4-yl) piperazin-1-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

- 17 -

13. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

5

14. A method for treating schizophrenia in a mammal, the method comprising administering to a mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

PCT

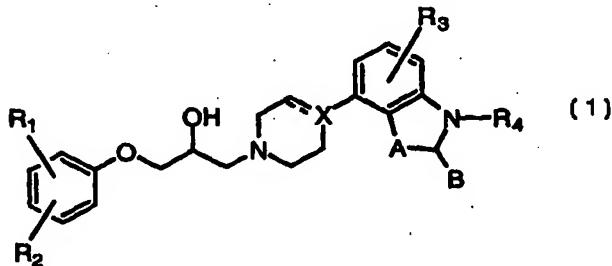
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :	A3	(11) International Publication Number: WO 99/55672 (43) International Publication Date: 4 November 1999 (04.11.99)
C07D 209/08, 209/34, 209/42, 403/12, A61K 31/40		
(21) International Application Number: PCT/US99/09132		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 28 April 1999 (28.04.99)		
(30) Priority Data: 09/069,129 29 April 1998 (29.04.98) US		
(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralta Farms, Madison, NJ 07940-0874 (US).		
(72) Inventors: KELLY, Michael, Gerard; 19 Clinton Court, Plainsboro, NJ 08536 (US). KANG, Young, Hee; 324 Andover Place, Robbinsville, NJ 08691 (US).		
(74) Agents: ECK, Steven, R.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.		
		(Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
		(88) Date of publication of the international search report: 20 January 2000 (20.01.00)

(54) Title: ANTIPSYCHOTIC INDOLYL DERIVATIVES



(57) Abstract

The present invention provides novel compounds of general formula (1), wherein R₁ and R₂ are H, OH, F, Cl, Br, I, 1 to 6 carbon alkyl or alkenyl, 1 to 6 carbon alkoxy, aryl, OR₅, nitro, amino, CF₃ or R₁ and R₂ are taken together to form a fused ring at the 1,2- or 2,3-positions providing a fused phenyl group or a benzodioxane group, or a 4- or 7-substituted indole group, or a 4- or 5- or 8-substituted quinoline group; R₃ represents a group selected from hydrogen, a 1 to 6 carbon alkyl or R₅; R₅ is CH₂Ph in which the phenyl ring can be optionally substituted by a group selected from OMe, halogen, CF₃; X is selected from a group represented by N, CR₄, CHR₄ and CHCH; A is selected from a group represented by N, NH, CH and CH₂; B is selected from a group represented by -O-, -S-, H and H₂; or A and B may be concatenated together to form indole, benzimidazole, indolone or indoline moieties; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions and methods of treating central nervous system disorders utilizing these compounds.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/09132

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D209/08 C07D209/34 C07D209/42 C07D403/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 722 941 A (E. LILLY AND CO.) 24 July 1996 (1996-07-24) claims 1-7,10 ----	1,13
Y	EP 0 169 148 A (ROUSSEL-UCLAF) 22 January 1986 (1986-01-22) claims 1,4-6,8,12,13; example 13 ----	1,13
A	WO 97 48698 A (E. LILLY AND CO.) 24 December 1997 (1997-12-24) claims 1,5 ----	1,13
A	US 4 335 126 A (A. KLEEMANN ET AL.) 15 June 1982 (1982-06-15) claims 1,29; example 18 ----	1,13 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 November 1999

Date of mailing of the international search report

22/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Intelli	nal Application No
PCT/US 99/09132	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. NIVAS RASTOGI ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 15, no. 3, 1972, pages 286-91, XP000674757 table II, compounds no. 15-30	1

In. International application No.

INTERNATIONAL SEARCH REPORT

PCT/US 99/09132

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1 iv PCT-Method for treatment of the human or animal body by therapy).

2. Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/09132

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 722941	A	24-07-1996	US 5576321 A AU 4651696 A BR 9607077 A CA 2210220 A CZ 9702207 A FI 973024 A HU 9901099 A JP 10512861 T NO 973281 A NZ 301161 A PL 321851 A WO 9622290 A US 5741789 A US 5627196 A US 5614523 A US 5789402 A	19-11-1996 07-08-1996 18-11-1997 25-07-1996 18-02-1998 16-07-1997 28-07-1999 08-12-1998 08-09-1997 28-10-1999 22-12-1997 25-07-1996 21-04-1996 06-05-1997 25-03-1997 04-08-1998
EP 169148	A	22-01-1986	FR 2567884 A JP 6057706 B JP 61037780 A US 4737505 A	24-01-1986 03-08-1994 22-02-1986 12-04-1988
WO 9748698	A	24-12-1997	AU 3401797 A CA 2257962 A EP 0814084 A US 5912256 A	07-01-1998 24-12-1997 29-12-1997 15-06-1999
US 4335126	A	15-06-1982	NONE	